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Systematic Review / Meta-analysis

"Impact of Vitamin C on Plasma Levels of Lipoprotein(a), Interleukin-6, and Fibrinolytic Activity" : A systematic review

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ABSTRACT

Ischemic heart disease remains a leading cause of global mortality, primarily attributed to atherosclerosis-induced blockage in the coronary arteries. A key contributor to atherosclerosis is the accumulation of lipoprotein(a), which functions akin to vitamin C in vascular matrix healing. Elevated lipoprotein(a) levels correlate with increased Interleukin-6 (IL-6) and reduced fibrinolytic activities, further exacerbating atherosclerosis. This review aims to elucidate whether vitamin C supplementation mitigates lipoprotein(a) levels, and IL-6 expression, and enhances fibrinolytic activities in both humans (CAD patients, type 2 diabetic patients, and healthy adults) and animal models (sepsis model of rats, transgenic mice, and wild type rats). A systematic search of Pubmed, Cochrane Library, and Google Scholar databases was conducted up to December 31, 2022, employing predefined selection criteria and a comprehensive search strategy. Of the 539 articles identified, 11 met the inclusion criteria, comprising 4 animal and 7 human studies. Animal trials demonstrated favorable outcomes with vitamin C supplementation, showing reductions in plasma lipoprotein(a) levels and decreased aortic accumulation of lp (a). Additionally, animals supplemented with vitamin C exhibited lower IL-6 production and enhanced fibrinolysis. Conversely, human studies reported no significant change in plasma lipoprotein(a) levels post-vitamin C supplementation (doses ranging from 500 mg to 4500 mg/day) in coronary artery disease (CAD) and healthy cohorts. However, supplementation did reduce serum IL-6 levels and increase fibrinolytic activities in both CAD and diabetic patients at doses between 1000 mg and 2000 mg of ascorbic acid. Vitamin C deficiency is prevalent among atherosclerosis patients, prompting lipoprotein(a) accumulation to counter intravascular scurvy in the absence of ascorbic acid. This review underscores the positive effects of vitamin C on atherosclerosis-associated factors, including lipoprotein(a), IL-6, and fibrinolytic activities. Optimal benefits are observed within the range of 1000 mg to 2000 mg/day, with higher doses conferring no additional advantages.

Introduction

Ischemic heart disease stands as a leading cause of mortality globally, stemming from the narrowing of coronary arteries or the formation of atherosclerotic plaques, a process persisting throughout life and claiming millions of lives annually. In the United States alone, coronary artery disease (CAD) claims approximately 370,000 lives each year. Notably, atherosclerotic plaque rupture triggers 75 % of ischemic heart attacks, with the highest incidence observed in individuals over the age of 45 for men and 50 for women [1,2].

The genesis of atherosclerotic plaques occurs when the endothelial linings of arteries sustain damage. Particularly critical is endothelial cell dysfunction at arterial curves and branches, where low shear stress and dispersed plasma flow prevail, facilitating plaque formation, see Fig. 1 [3,4,9]. These regions comprise both atherosclerotic susceptible and resistant areas within the endothelial wall [5]. In regions sensitive to atherosclerosis, endothelial cells exhibit a thin glycocalyx layer, cuboidal shape, and disorganized alignment [6]. Conversely, high laminar shear stress in resistant zones triggers the upregulation of Kruppel-like factors 2 and 4, leading to increased expression of endothelial nitric oxide synthase (eNOS) and thrombomodulin synthesis [7]. This serves as a deterrent to atherogenic lipoprotein detention. However, areas characterized by low levels of eNOS and superoxide dismutase are prone to atherogenic lipoprotein accumulation [8].

Atherosclerosis and lipoproteins containing apolipoprotein-B: ApoB-accommodating lipoproteins, including lipoprotein(a) (Lp(a)), LDL, VLDL, and IDL, are closely associated with the development of atherosclerosis. These atherogenic lipoproteins, characterized by their outer layer composed of ApoB, contribute significantly to the progression of atherosclerosis [10].

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In regions of the vasculature prone to atherosclerosis, where laminar flow is poor and shear stress is low, humoral and parietal stimuli may further promote atherogenesis [10]. ApoB-containing lipoproteins can penetrate the endothelial lining at these susceptible sites and infiltrate the intima space. Here, they become trapped due to interactions between positively charged residues such as arginine and lysine on ApoB and negatively charged sulfate groups on endothelial proteoglycans [11]. Once entrapped in the endothelial matrix, apoB-containing lipoproteins initiate a cascade of biochemical reactions, attracting macrophages, platelets, oxidized lipids, and cytokines to form atherosclerotic plaques [12]. Among these apoB-containing lipoproteins, Lp(a) holds particular significance in atherosclerosis progression [13].

Lipoprotein(a), discovered by Norwegian doctor Kre Berg in 1963, shares structural similarities with fibrinogen and plasminogen [14]. It is well-established for its role in thrombosis and atherosclerosis pathogenesis. Lp(a) contributes to atherosclerosis progression through various mechanisms, including the induction of endothelial cell adhesion molecule-1 and E-selectin expression in susceptible endothelial cells. Additionally, Lp(a) promotes the proliferation of peripheral plasma mononuclear cells in vessels and acts as a pro-inflammatory molecule via its oxidized phospholipids [15]. High levels of apo(a) in atherosclerotic plaque stains further underscore the significant deposition of Lp(a) in plaques [16]. Recent findings have linked Lp(a) levels exceeding 50 mg/dl to a 60 % increased risk of atherosclerosis development, independent of LDL-cholesterol levels, according to data from the Multi-Ethnic Study of Atherosclerosis (MESA) [17].

Table 1, 2, 3.

Vitamin C and Atherosclerosis: Vitamin C protects the vasculature from free radicals and aids metabolism and immunity. Since it donates electrons and is structurally similar to glucose (see Fig. 2 and Fig. 3).

Previous research has indicated a strong correlation between vitamin C deficiency and hypertension, which is a significant risk factor for the development of intimal capillary hemorrhage and plaque formation [18]. Dr. G.C. Willis further investigated this link using guinea pigs and confirmed Paterson's findings, demonstrating that vitamin C deficiency is indeed associated with atherosclerosis [19]. Willis also highlighted that the location of atherosclerosis depends on the mechanical pressure exerted on the artery walls, influenced by factors such as blood pressure, tissue pressure, artery curvature, and arterial fixation [20]. In a subsequent clinical study conducted in 1954, Willis administered three daily doses of 500 mg of vitamin C orally to participants and observed a reduction in atherosclerotic plaques in individuals, suggesting a potential therapeutic effect of vitamin C in treating atherosclerosis [21].

Further investigation revealed that vitamin C deficiency can lead to increased activity of HMG-CoA reductase, resulting in elevated cholesterol production [22]. Conversely, high levels of vitamin C act as a natural statin, reducing the activity of HMG-CoA reductase and thereby lowering cholesterol synthesis [23].

Moreover, vitamin C deficiency has been associated with a higher risk of atherosclerotic progression due to increased oxidation of LDL-C in the presence of low plasma ascorbate levels. Additionally, low vitamin C status is linked to decreased plasminogen activation, resulting in lower fibrinolytic activity [24]. Reduced vitamin C levels also contribute to endothelial dysfunction, leading to enhanced adhesion and migration of monocytes to the arterial wall. Vitamin C is essential for collagen formation, a critical component of the arterial wall matrix. Its deficiency can impair collagen synthesis, weakening the arterial wall and facilitating monocyte adhesion and migration, thereby increasing the production of inflammatory markers such as IL-6 [25].

Vitamin C and Lipoprotein(a): Humans ceased producing vitamin C 60 million years ago when the gulonolactone oxidase enzyme stopped being produced in humans, which is a crucial enzyme used to convert glucose to ascorbate in humans [26]. Scientists Matthias Rath and Linus Pauling proposed a hypothesis that states that lipoprotein(a) acts as a surrogate for ascorbate. They hypothesized that lp(a) aims to safeguard the vascular wall integrity in vitamin C deficiency by depositing itself on the vasculature. Vascular deposition of lp(a) can prevent microhemorrhages from scurvy [27]. It has been evident that prolonged nutritional scarcity of ascorbic acid makes lipoprotein(a) do its work and lp(a) starts to behave as ascorbate and helps wound healing at the intravascular level by depositing itself on the vascular matrix which further initiates the development of atherosclerotic plaques on endothelium wall [28].

Role of Lp(a) In Atherosclerosis: Although the precise role of lipoprotein(a) (lp(a)) in atherosclerosis remains elusive, elevated serum levels have consistently been associated with coronary atherosclerosis (CAD), suggesting its potential involvement in disease pathogenesis. Several mechanisms have been proposed to explain lp(a)'s contribution to atherosclerosis.

One proposed mechanism suggests that lp(a) is directly deposited at the arterial walls of atherosclerotic susceptible regions. Scavenger receptors fasten the absorption of lp(a) into the macrophages because lp(a) is more probable to be oxidized than LDL [30]. Another possible mechanism is related to the inverse correlation between the lp(a) level and the vascular reactivity. In this mechanism, elevated plasma lp(a) can result in endothelial dysfunction [31]. Lp(a) contains all the pro-atherogenic characteristics of LDL-cholesterol but in addition to that, it contains apo(a), a phospholipid sink that facilitates lp(a)'s pro-atherogenic capabilities, particularly its inflammatory features [32].

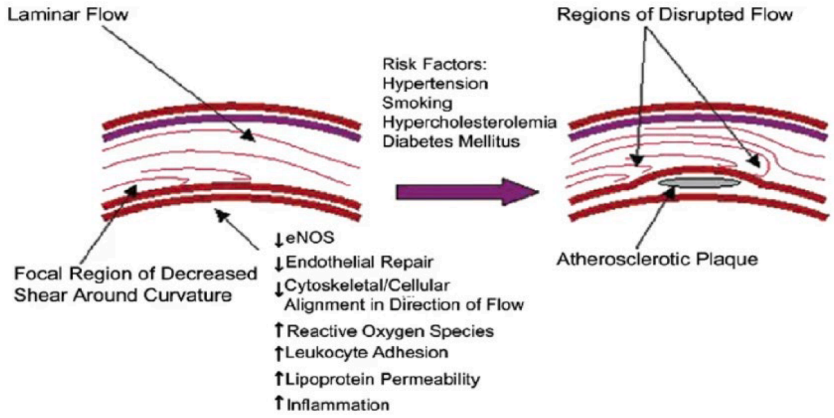

Fig. 1. Low laminar plasma shear stress around curves causes atherogenesis in endothelial cells.
Source: Cunningham et al. [86].

Table 1
Literature Summary Table.

Author/ year	Sample species	Type of Study	Intervention	Dose/route	Patient/ population	Control	Findings
Jenner et al. [61], 1999	Human	RCT	Vitamin C	1 g/oral	101 Healthy adults	Placebo	No change in serum lp(a) conc.
Boston AG et al. [62], 1995	Human	RCT	Vitamin C	4.5 g/oral	44 CAD	Placebo	Plasma lp(a) levels were not altered.
C.Antonia des et al. [63], 2003	Human	RCT	Vitamin C	2 g/oral	37 T2DM/CAD	no-antioxi Dant	No change in serum IL-6 levels
Mohammed et al. [64], 2015	Human	RCT	Vitamin C	1 g/oral	64 hypertensi ve/ T2DM	No supplem-e ntation	Significant reduction in serum IL-6 levels
C.Antonia des et al. [63], 2003	Human	RCT	Vitamin C	2 g/oral	39 T2DM/CAD	No antioxida nt	Decrease in plasma fV and tPA. No change in protein S, protein C, fVII, ATIII and PAI-1.
AK Bordia et al. [65], 1980	Human	Clinical trial	Vitamin C	1 g and 2 g oral	80 CAD	placebo	Significant dose-response increase in fibrinolytic activities.
DK Paliwal et al. [66], 1978	Human	RCT	Vitamin C	1 g and 2 g oral	40 healthy/CAD	Placebo	Significant increase in fibrinolysis
Gary P Van Guilder et al. [67], 2008	Human	Clinical trial	Vitamin C	500 mg oral	17 obese	No treatment	Increase in endothelial tPA release but no change in arterial or venous tPA antigen.
John Cha et al. [68], 2015	Animal	RCT	Vitamin C	2.75 mg oral	Gulo-/-:lp(a)+ transgenic mice	0.15 mg and 0.30 mg vitamin C	lp(a) deposits were found in atherosclerotic plaques in hypo ascorbic mice but no plaques were found in vitamin C supplementation mice.
M.Rath et al. [69], 1990	Animal	RCT	Vitamin C	40 mg/kg oral	Guinea pigs	No vitamin C	Vitamin C supplementing pigs do not have atherosclerotic plaques but low vitamin c pigs do develop plaques and lp(a) deposited in them.
Ningzhang et al. [70], 2021	Animal	Clinical trial	Vitamin C	Unknown oral	Septic rats	bradykinin	Vitamin C reduced serum IL-6.
Hyejung et al. [71], 2022	Animal	Clinical trial	Vitamin C	unknown/I. P	Acute colitis mouse	No treatment	Vitamin C reduces IL-6 production"

Table 2
For each characteristic in the SYRCLE risk of bias tool, this table displays the corresponding risk of bias assessment markers.

		John et al. [68]	M.Rath et al. [69]	Ning Zhang et al. [70]	Hyejung et al. [71]
Selection Bias	Sequence generation@@@@Baseline characteristics@@@@Allocation concealment	+@@@@. @@@@.	+@@@@. @@@@.	+@@@@. @@@@.	?@@@@. @@@@.
Performance bias	Random housing@@@@Blinding	–@@@@?	–@@@@.	+@@@@?	–@@@@N.A
Detection bias	Random outcome assessment@@@@Blinding	+@@@@N.A	?@@@@?	+@@@@N.A	+@@@@N.A
Attribution bias	Incomplete outcome data	.	.	.	.
Reporting bias	Selective outcome reporting	+	+	+	+
Other types of bias		.	.	.	.

(-)shows a significant possibility of prejudice, (+) denotes a minimal possibility of bias, Uncertain bias risk is indicated by (?). (N.A) represents not applicable.

Table 3
Clinical changes in treatment and control groups before and after giving each group 1 *g* of vitamin C daily.

Characteristic	Vitamin C ($n = 31$) (Before)	Vitamin C ($n = 31$) (After)	Control ($n = 33$) (Before)	Control ($n = 33$) (After)	P-value
hs-CRP (mg/L)	14.8 ± 9.2	7.7 ± 4.5 *	14.50 ± 14.26	11.81 ± 7.33	0.01 **
IL-6 (pg/mL)	2.20 ± 0.75	1.4 ± 0.5 *	1.95 ± 0.75	2.01 ± 0.87	0.001 **
TC (mg/dL)	207.7 ± 36.2	196.5 ± 33.9	211.03 ± 39.04	213.4 ± 38.7	0.071
TG (mg/dL)	223.8 ± 87.8	155.10 ± 48.12 *	202.91 ± 107.00	183.45 ± 95.82 *	0.138

Source: Mohammed et al. [64].
* Significant change observed at $p = 0.05$ (2-tailed paired sample *t*-test).
** Significant difference observed at $p < 0.001$ (2-tailed independent sample *t*-test).

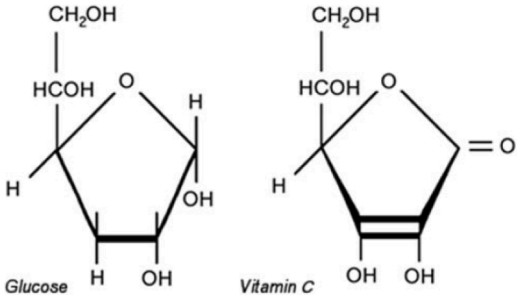

Fig. 2. The structural similarities between glucose molecules and ascorbic acid.

Another critical mechanism involves the impairment of fibrinolytic activities induced by higher lp(a) levels. Fibrinolysis, essential for clot dissolution, is hindered when lp(a) inhibits plasminogen activation. Apo (a) competes with plasminogen for binding sites on fibrin, diminishing plasmin formation and hindering the attachment of plasmin to fibrin. Additionally, lp(a) reduces the activity of tissue plasminogen activator, further impeding the conversion of plasminogen to plasmin [24].

Overall, lp(a) plays a multifaceted role in atherosclerosis, involving its deposition in arterial walls, promotion of endothelial dysfunction, exacerbation of inflammation, and impairment of fibrinolysis. These mechanisms collectively contribute to lp(a)'s pro-atherogenic properties and its association with CAD.

Role of other factors in Atherosclerosis associated with Lp(a): An inflammatory signal called Interleukin-6 (IL-6) and poor fibrinolysis are two of the many important variables that contribute to the formation and propagation of atherosclerotic plaques associated with lp(a).

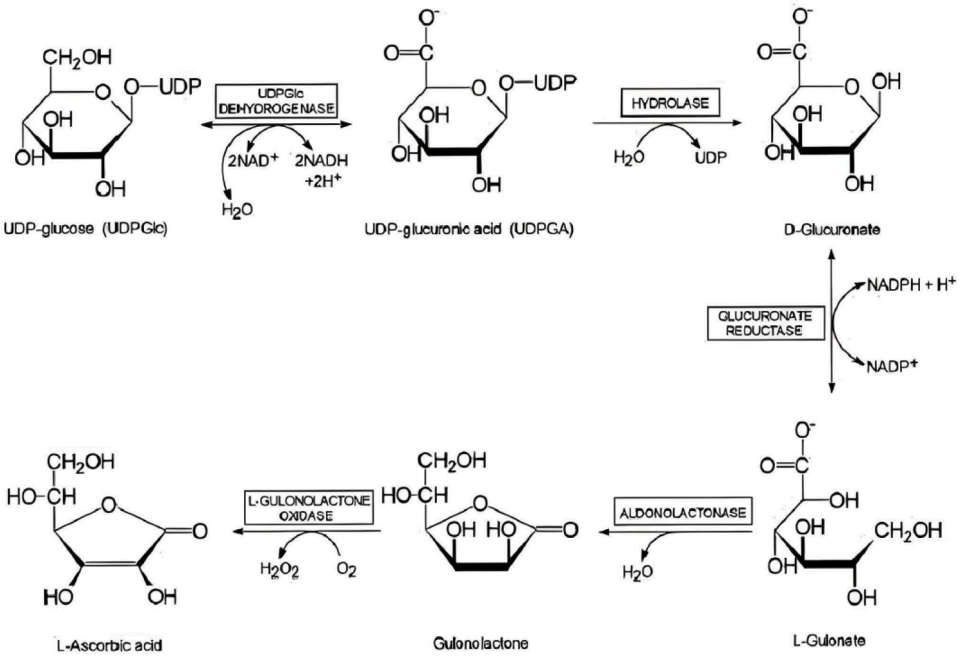

Fig. 3. L-Gulonolactone oxidase generating vitamin C from glucose molecules. Source: Dr. Joao Oiano Neto,2008 [29].

The link between lp(a) and IL-6: The presence of a class II IL-6 response element (CTGGGA) in the LPA gene, known to enhance apo (a) production, underscores the direct relationship between lipoprotein (a) (lp(a)) and interleukin-6 (IL-6) [33]. Numerous investigations have highlighted the association between increased lp(a) levels and IL-6 during acute phase responses [34,35]. A genetic analysis involving 2331 subjects revealed a correlation between a single nucleotide polymorphism (SNP) in the IL-6 gene (−174 G/C) and baseline lp(a) concentrations [36].

Moreover, Muller et al. [37]. demonstrated a significant correlation between LPA gene expression and IL-6-mediated acute phase response biomarkers, such as C4b binding protein and complement C9, through liver biopsy analysis in 57 subjects. Subsequent experimentation involving the incubation of human hepatocytes with IL-6 resulted in a notable upregulation of hepatic LPA gene expression at both protein and mRNA levels. Further supporting this relationship, incubation of hepatocytes with tocilizumab, a monoclonal antibody targeting IL-6 receptors, led to a reduction in apo(a) protein levels and downregulation of LPA mRNA expression, consequently lowering lp(a) concentrations [37].

Role of IL-6 in atherosclerosis: IL-6 plays a pivotal role in the progression of atherosclerosis by influencing various cellular and molecular pathways. One crucial aspect is its impact on the activation and proliferation of T-cells, which play a central role in driving immune responses against peptide epitopes associated with atherosclerosis, including those derived from apolipoprotein B, a component of lipoprotein(a) [38,39].

Furthermore, IL-6 induces the synthesis of acute-phase proteins in hepatocytes, such as C-reactive protein (CRP) and amyloid proteins, which are associated with atherosclerosis [40,41]. IL-6 also acts as a chemotactic activator for neutrophils and macrophages, leading to increased recruitment of these cells to the sites of inflammation and atherosclerotic lesions [42–44].

The STAT3 pathway, which is activated by IL-6, plays a significant role in mediating cellular responses in atherosclerosis [45]. Specifically, the STAT3α isoform has been implicated in accelerating atherosclerosis progression by downregulating anti-inflammatory genes [46]. Moreover, IL-6-mediated activation of the JAK/STAT3 pathway upregulates the expression of monocyte chemotactic protein-1 and other pro-inflammatory markers, exacerbating the inflammatory response associated with atherosclerosis [47].

IL-6 also exerts direct effects on various cell types involved in atherosclerosis, including smooth muscle cells [48], and stimulates the growth and activation of endothelial cells [49], and platelets [50]. Through trans-signaling, IL-6 promotes endothelial cell activation and upregulates the expression of cell adhesion molecules, such as VCAM-1, ICAM-1, and E-selectin, facilitating the recruitment and adhesion of monocytes to the endothelium, where they differentiate into macrophages and contribute to the formation of foam cells within the subendothelial space [51–53].

Inhibition of IL-6 trans-signaling has been shown to mitigate atherosclerotic lesion progression. Studies utilizing IL-6 fusion proteins and trans-signaling inhibitors demonstrated a reduction in endothelial adhesion molecule expression and macrophage accumulation in atherosclerosis-prone mice, leading to attenuation of atherosclerotic progression [54]. Additionally, reducing IL-6 levels has been associated with decreased levels of CRP and fibrinogen, which are known risk factors for coronary artery disease risk [55].

Impaired fibrinolysis and atherosclerosis: The apo(a) component of lp(a) shares structural similarities with plasminogen, featuring kringle domains similar to plasminogen's K4 and K5. Apo(a) contains 10 kringle IV (KIV) repeats, designated as KIV1 to KIV10, each with slight

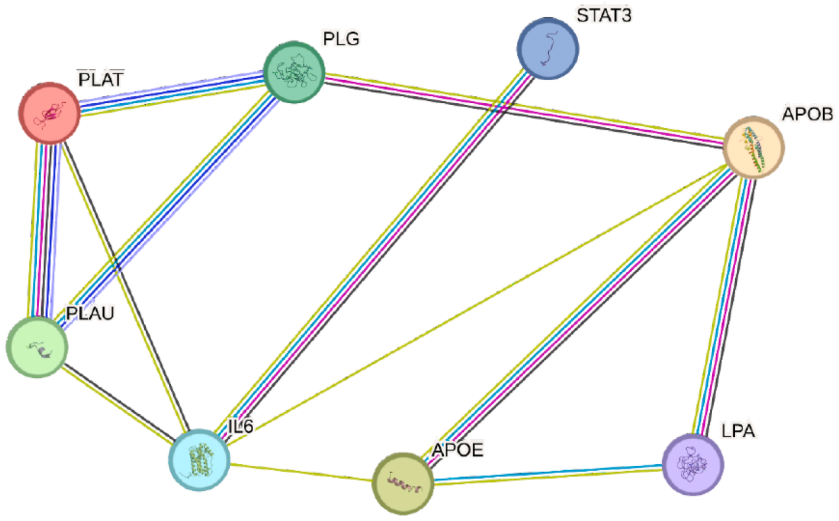

Fig. 4. we have extracted the interactions between these 8 proteins at a high confidence level, keeping interactions only at the query level. PLAT- tissue-type plasminogen activator, LPA- lipoprotein(a), PLG- plasminogen, PLAU- Urokinase-type plasminogen activator, APOE- ApolipoproteinE, APOB- ApolipoproteinB-100, IL-6– Interleukin6, STAT3 is a pathway associated with atherosclerosis and inflammation. As the image shows, all the query proteins are interlinked to each other either directly or indirectly showing that all the proteins are affecting each other's functionality and quantity.
Source: Szklarczyk et al. string (2015) [60].

amino acid variations. These KIV repeats influence the size of lp(a) isoforms, with weak lysine receptor regions in KIV 5–8 facilitating initial non-covalent binding between apo(a) and apoB-100 during lp(a) assembly [5]. Additionally, the unpaired cysteine residue in KIV9 forms a disulfide bond with apoB-100, while the strong lysine receptor in KIV10 enhances lp(a)'s binding to exposed lysine residues on fibrin surfaces [56].

Lp(a) has been demonstrated to inhibit fibrinolysis in both in vitro and in vivo studies [57]. Interactions between lp(a) and various fibrinolytic factors, such as fibrinogen, plasmin-modified fibrinogen, plasminogen, and tissue-type plasminogen activator (tPA), have been observed. Early research showed that lp(a) prevents plasminogen and tPA from binding to fibrin, though the precise mechanism by which the apo(a) moiety of Lp(a) inhibits plasminogen activation remains a subject of debate, with both competitive and uncompetitive mechanisms proposed [58,59]. As evident in Fig. 4, we used string database [60] to show the interaction between various proteins responsible in developemt of atherosclerosis..

In this systematic review, we have reviewed clinical trials in which intervention was only Vitamin C and not with a combination of any other drug or nutrient. The patients we have focused on are either healthy patients or patients who are at risk of developing atherosclerosis, such as hypertensive, obese, or type 2 diabetic patients or CAD patients. The articles we have reviewed are clinical trials on both animal and human subjects in which vitamin C was intervened orally.

To the best of our knowledge, no review has focused on vitamin C's effect on all the factors promoting atherosclerosis that are linked to lipoprotein(a). No other review has been focused on lipoprotein(a) levels, impaired fibrinolysis, and IL-6 levels in the blood, which are all interlinked to each other. There was a requirement for such a review in which all aspects of atherosclerosis influencing factors related to lipoprotein(a) in which a common micronutrient was intervened. Hence, it is the first review that has focused on vitamin C's role in lipoprotein(a) and its linked factors that can promote atherosclerosis, which is IL-6 and impaired fibrinolysis. This review aims to find out whether or not high-dose vitamin C intervention reduces lipoprotein(a) and IL6 concentration along with an increment in fibrinolytic activities in both human and animal subjects.

Methodology

Eligibility criteria and search strategy

We conducted a comprehensive search across three databases—PubMed, Google Scholar, and Cochrane Library—using specific keywords related to vitamin C, atherosclerosis, lipoprotein(a) (Lp(a)), interleukin-6 (IL-6), and fibrinolytic activity. The search was limited to original papers published in English until December 31, 2022. The search strategy was last implemented on 8 July 2023.

Following PRISMA guidelines, we identified relevant animal and human studies, excluding duplicate articles. Abstracts were screened to select in vivo studies, with a focus on clinical trials. Studies involving interventions other than vitamin C, such as micronutrients or pharmaceuticals, were excluded. Similarly, studies involving subjects unrelated to coronary artery disease (CAD) or its risk factors were also excluded.

Included human studies comprised CAD patients, individuals at risk of CAD (e.g., diabetic, obese, hypertensive), and healthy subjects. Animal studies included those where animals synthesized human Lp(a) or apo(a), such as guinea pigs and transgenic mice, and those with elevated plasma IL-6 levels.

The search strategy involved screening references of excluded papers to identify any additional relevant articles. This ensured a comprehensive review of primary and secondary sources. The screening process adhered to predefined inclusion criteria, focusing on vitamin C intervention in the context of atherosclerosis and associated risk factors.

The search and screening strategy is outlined in Fig. 5for clarity and transparency.

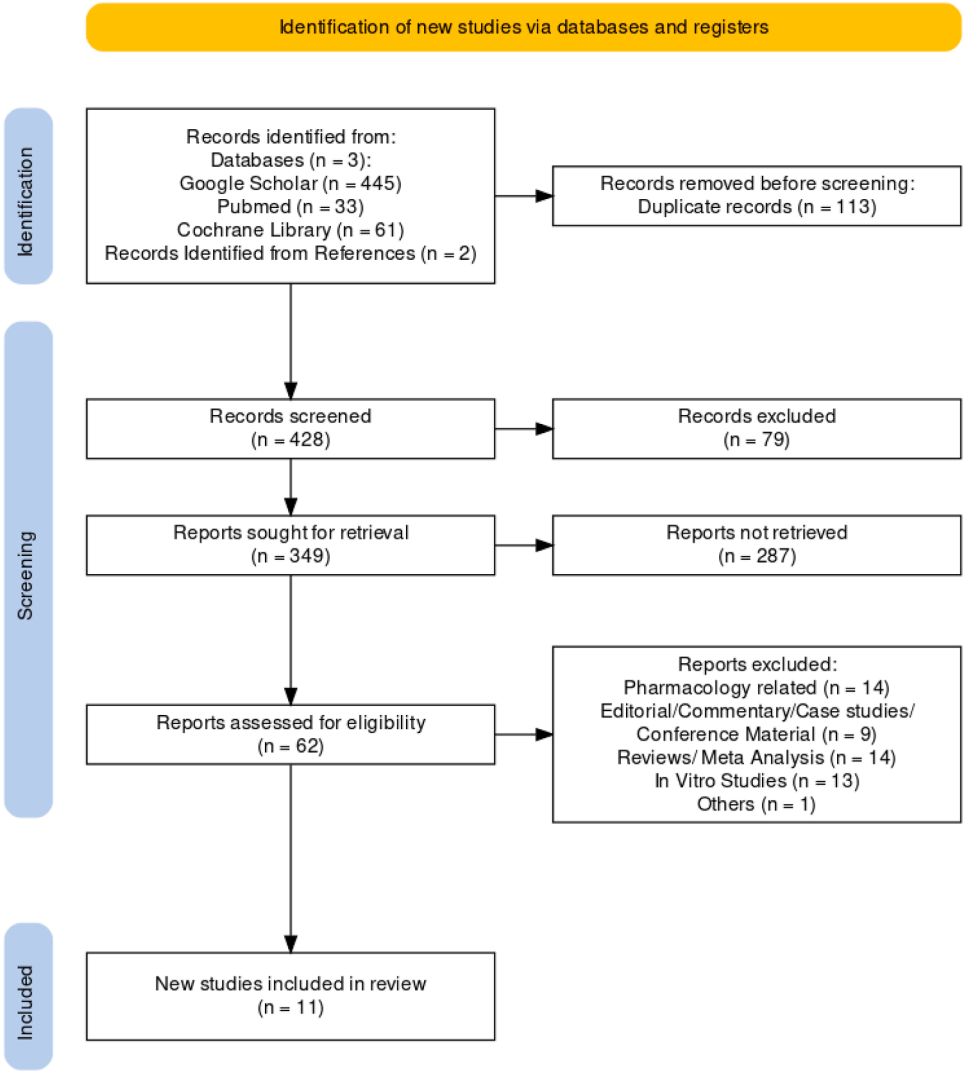

Fig. 5. Literature search and selection protocol according to the PRISMA flow diagrams.

Study selection

This review focuses on clinical trials investigating the therapeutic potential of vitamin C supplementation in individuals with coronary artery disease (CAD), obesity, type 2 diabetes, hypertension, or those at risk of atherosclerosis. We included studies involving both human subjects and animal models with experimentally induced atherosclerosis or elevated levels of lipoprotein(a) (lp(a)) and interleukin-6 (IL-6).

Only clinical trials using oral or intraperitoneal administration of vitamin C were considered, while studies involving intravenous administration were excluded. We specifically targeted trials measuring lp(a), IL-6 levels, and fibrinolytic activities after vitamin C treatment in individuals with atherosclerosis or its risk factors.

A total of 11 papers were included for review, consisting of 7 human clinical trials and 4 animal studies, as shown in Table 1. Human trials focused on plasma lp(a) levels, IL-6 levels, and impaired fibrinolytic activities following vitamin C supplementation. Similarly, animal studies investigated the impact of vitamin C on lp(a) and IL-6 levels.

We excluded studies involving subjects unrelated to CAD or atherosclerosis risk and those not solely assessing the effects of vitamin C intervention. Additionally, in vitro studies focusing on fibrinolytic activity in endothelial cells were excluded.

Overall, the selected studies provide insights into the potential therapeutic role of vitamin C in mitigating factors associated with atherosclerosis progression.

Data extraction

Two independent reviewers screened all studies based on authors, study design, participant characteristics, response criteria, intervention type, mode, and outcome measured. The sample was divided into animal and human studies for clarity and ease of communication.

Quality of bias assessment

For human studies, we have used the CASP tool(Critical Appraisal

Skills Programme (2018)(165). We have only kept those studies to review which scores at least 50 % (refer to appendix 1). For animal studies included, we have used the SYRCLE RoB tool(Systematic Review Renter for Laboratory Animal Experimentation,(2014) [73]) to assess the quality of papers, see Table 2. We have only kept those papers that scored at least 5 marks out of 10.

Results

The results are shown below differently for animal and human studies for the sake of ease of understanding and differentiation.

Human studies

Vitamin C and lp(a) level

Human studies have shown no change in serum lipoprotein(a) level after various doses of the vitamin C intervention. Jenner et al. [61], in 1999, examined the effectiveness of vitamin C on plasma lp(a) levels. In this study, they included 138 people, out of whom only 101 patients provided blood to calculate plasma lp(a) concentration. People who were smokers, had heart disease, liver disease, or diabetes, taking any lipid-lowering drug and ascorbic acid supplementation were excluded from the trial. People were randomized into two groups: the intervention group($n = 49$) and the placebo group($n = 51$). People in the intervention group received 2 tablets of 500 mg of ascorbic acid per day and people in the placebo group received matching placebo tablets to take for 8 months. In both groups, the baseline plasma lp(a) measurement was 0.110 mg/l ($p = 0.71$). The geometric mean baseline lp(a) levels in both the placebo and treatment group were 0.095 mg/l and 0.099 mg/l, respectively. 35 subjects had >0.050 g/l lp(a) levels, out of which 17 were in the placebo group and 18 were in the intervention group. After 8 months of intervention, Jenner et al. [61]. found no difference in the lp(a) level in both groups. Moreover, subjects were dichotomized into 2 groups according to their baseline plasma ascorbic acid(PAA) level to test whether plasma ascorbic concentration had any effect on lp(a) concentration after 8 months of intervention or not. One group had a baseline PAA concentration of <55 umol/l ($n = 61$) and the other group had a PAA level of >55 umol/l ($n = 40$). After 8 months, no difference was found in lp(a) concentrations in both groups.

A Similar result was observed by AG Bostom et al. [62]., in 1995, when they intervened with 4.5 g of vitamin C every day in their randomized controlled trial with 44 patients for 12 weeks. The patients included were all adults who had developed at least 50 % or more stenosis in one of the major coronary arteries before the age of 60. They were given 4.5 *g* of vitamin C per day vs placebo for 12 weeks. After 12 weeks of continuous supplementation, they also found no significant changes in the blood lp(a) concentration in both groups [$p = 0.39$].

Vitamin C and IL-6

The effectiveness of vitamin C in modulating IL-6 plasma levels has yielded inconsistent findings in the literature. Antoniades et al. [63]. conducted an intervention study involving 37 subjects diagnosed with both type 2 diabetes and coronary artery disease. These individuals, who met specific inclusion criteria, were randomized into either a treatment group receiving 2 g/day of vitamin C ($n = 17$) or a control group receiving no antioxidant treatment ($n = 18$) for 4 weeks. ELISA was employed to measure serum IL-6 levels before and after the intervention. Despite the administration of vitamin C, no significant changes in IL-6 levels were observed within the treatment group ($p > 0.05$). Conversely, Mohammed et al. [64], investigated 62 patients with hypertension and diabetes, randomized into intervention ($n = 31$) and control ($n = 31$) groups. The intervention group received 1 g/day of vitamin C for 8 weeks, while the control group received no supplementation (see Table 3). Notably, a significant reduction in IL-6 serum concentration was observed in the vitamin C group ($p < 0.001$), contrasting with the control group where IL-6 levels showed no significant change ($p > 0.05$). These findings underscore the variability in the effects of vitamin C on IL-6 levels, warranting further investigation into its mechanisms of action and clinical implications.

Vitamin C and fibrinolytic activities

The utilization of high-dose vitamin C supplementation as a means to enhance fibrinolysis and improve vascular function presents a compelling avenue for therapeutic intervention. Antoniades et al. [63]. conducted a study involving 39 patients diagnosed with type 2 diabetes and coronary artery disease (CAD), characterized by at least one coronary stenosis exceeding 50 %, as confirmed by angiography. Patients with baseline HbA1c levels below 7 % and normal blood pressure (<140/90) were included in the study. They were randomly assigned to either a treatment group ($n = 19$), receiving 2 *g* of vitamin C daily, or a control group ($n = 20$) receiving no antioxidant supplementation. After a 4-week intervention period, plasma levels of tissue plasminogen activator (tPA) and factor V (fV) were measured.

Significantly reduced plasma fV levels were observed in the treatment group compared to baseline ($p = 0.038$), while no significant change was noted in the control group ($p = 0.661$). Additionally, a notable difference in plasma fV levels between the treatment and control groups was evident ($p = 0.596$). Furthermore, plasma von Willebrand factor (vWF) levels were significantly decreased in the treatment group ($p = 0.016$), whereas no significant change was observed in the control group ($p = 0.665$). Importantly, the treatment group exhibited a significantly greater reduction in plasma vWF levels compared to the control group ($p = 0.036$). These findings underscore the potential of high-dose vitamin C supplementation in modulating fibrinolysis and improving vascular health, thus warranting further exploration in clinical practice.

In another trial by A.K. Bordia et al. [65] in 1980, two parts of research were conducted. The first part involved 40 patients with a history of coronary episodes, randomized into three groups receiving different doses of vitamin C for 6 months. Results showed that both moderate (1 g/day) and high (2 g/day) doses of vitamin C led to significant increases in serum fibrinolytic activity compared to the control group. In the second part, 40 patients with acute myocardial infarction were randomized to receive vitamin C or placebo. Vitamin C supplementation significantly increased fibrinolytic activity by 62.5 % ($p < 0.001$), with a decline observed after discontinuation of vitamin C. No significant change was observed in the placebo group.

Similarly, in a study by D.K. Paliwal et al. [66] in 1978, fibrinolytic activity significantly increased in healthy individuals and CAD patients after vitamin C administration. However, fat administration attenuated the increase in fibrinolytic activity. Additionally, a study by Guilder et al. [67] in 2015 showed that oral supplementation with vitamin C increased endothelial tPA release in response to bradykinin, indicating a potential role in endothelial function regulation.

Overall, these trials highlight the potential of vitamin C

supplementation in enhancing fibrinolysis, particularly in individuals with cardiovascular risk factors.

Animal studies

Vitamin C and lp(a)

Various animal models have been studied to check whether vitamin C has any effect on circulating lp(a) level or not, such as guinea pigs, GULO-/-, lp(a)+/+ transgenic mice, and sepsis models.

Transgenic GULO-/-, lp(a)+/+ mice, lacking the gulonolactone oxidase enzyme gene responsible for vitamin C synthesis but possessing the gene for producing human lipoprotein(a) (lp(a)), serve as a valuable model for studying the interplay between lp(a) and vitamin C deficiency in atherosclerosis development. These mice were developed through crossbreeding involving GULO -/- mice with human apo(a) strain mice and GULO -/- mice with human apoB-100 strain mice. Subsequent crossbreeding between these strains produced the GULO -/-, lp(a)+ strain, which lacks endogenous vitamin C synthesis but expresses human lp(a).

Vitamin C's impact on lp(a) producing transgenic mice

Cha et al. [68] conducted experiments using two strains of mice: Gulo -/- and Gulo-/-; lp(a)+. The Gulo -/- mice lack the lp(a) gene and cannot synthesize lp(a). They were divided into two groups: one receiving 2.75 mg/day of vitamin C and the other receiving no vitamin C, leading to complete ascorbic acid depletion within 8 weeks. Meanwhile, the Gulo-/-; lp(a)+ mice were grouped into three, receiving 0.15 mg/day, 0.30 mg/day, and 2.75 mg/day of vitamin C over 12 weeks. Female mice consistently exhibited higher lp(a) concentrations compared to males. Gulo-/- mice receiving 2.75 mg/day of vitamin C showed no lp(a) production, while those deprived of vitamin C synthesized lp(a) and succumbed to scurvy-like symptoms. Additionally, lp(a) levels significantly decreased due to reduced protein synthesis in this metabolic disorder state, with male and female Gulo-/- mice producing 8.6 ± 5.6 mg/dl lp(a).

In Gulo -/-, lp(a)+ mice, lp(a) concentration inversely correlated with ascorbic acid supplementation. Among the three groups receiving different doses of vitamin C, those receiving 2.75 mg/day produced significantly less lp(a) compared to the 0.15 mg/day and 0.30 mg/day groups ($p < 0.05$).

In addition to human apoB-100, mice also produce their own apoB-100. Cha et al. (2015) noted that the group receiving 2.75 mg of vitamin C exhibited lower levels of human apoB-100 in both male and female mice, while there was minimal difference in mouse apoB-100 levels across all groups.

Further investigation revealed that early atherosclerosis development was linked to lp(a) accumulation within the inner layers and deeper regions of the blood vessel walls. Male mice consuming 2.75 mg of vitamin C showed no lp(a) deposition in their vascular walls, whereas female mice did. Conversely, in mice with low or no vitamin C in their diet, lp(a) deposition was evident in the arterial walls, as detected by immunohistochemical co-localization of apoB-100, apo(a), and fibrinogen. These mice also exhibited elastin degradation within their vascular walls alongside lp(a) deposition.

Matthias Rath and Linus Pauling [69] employed guinea pigs to investigate the role of vitamin C in lp(a) accumulation in atherosclerotic lesions, given their propensity to develop atherosclerotic plaques and their inability to synthesize vitamin C, akin to humans. Guinea pigs also produce lp(a) similar to humans. Sixteen male guinea pigs were divided into two groups: one receiving 40 mg/kg/day of ascorbic acid along with vitamin C-free guinea pig chow (Purina) and the other receiving only 2 mg/kg/day of ascorbic acid to induce hypoascorbemia along with ascorbate-free Purina.

After five weeks, the animals were euthanized, and their heart, aorta, and various organs were collected for biochemical and histological analysis. Immunoreactivity for apo(a) was detected in hypoascorbic pigs, indicating lp(a) metabolism in the absence of vitamin C. Furthermore, immunoreactivity for apo(a) was observed in the atherosclerotic lesions of the aorta, suggesting lp(a) deposition in the plaque under hypoascorbemia conditions. This observation was not evident in pigs receiving 40 mg of vitamin C.

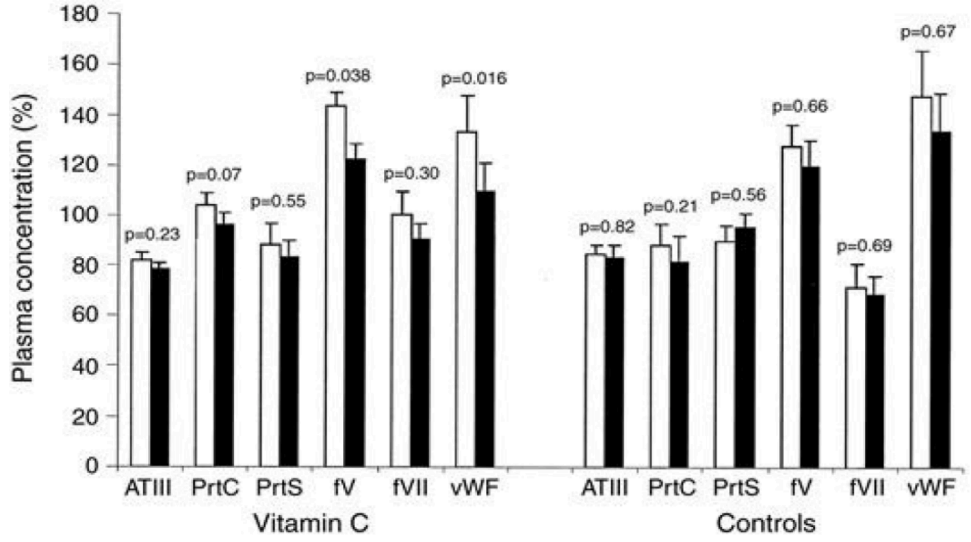

Fig. 6. The graph, from Antoniades et al. [63], illustrates the impact of vitamin C supplementation on plasma levels of von Willebrand factor (vWF), antithrombin III (ATIII), protein C (prtC), protein S (prtS), factor V (fV), and factor VII (fVII) in patients with type 2 diabetes and concomitant coronary artery disease (CAD). Notably, only the vitamin C treatment group exhibited significantly reduced plasma levels of fV and vWF ($P < 0.05$ for both), while no significant changes were observed in the control group. Moreover, the reduction in vWF levels within the vitamin C treatment group was statistically higher compared to the control group ($P = 0.036$). Conversely, concentrations of ATIII, prtC, prtS, and fVII remained constant in both treatment and control groups. These findings underscore the selective effectiveness of vitamin C in modulating key biomarkers associated with vascular health in diabetic patients with CAD.
* Before therapy; □ following treatment. Means and SE are used to express data.

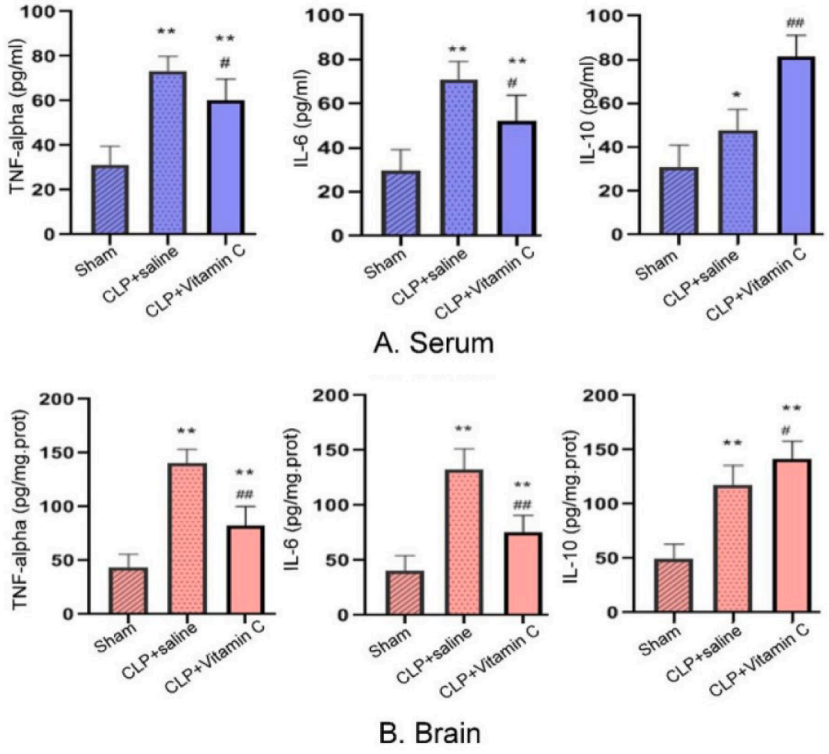

Fig. 7. In the study by Ningzhang et al. (2022) [70], the comparison of TNF-alpha, IL-6, and IL-10 levels was conducted 3 hours post-operation in both serum (A) and brain (B). The levels of these inflammatory cytokines were notably elevated in both the CLP + saline and vit *C* + CLP groups compared to the sham group rats ($p = 0.001$). However, the CLP + vit C group exhibited significantly lower levels of TNF-alpha and IL-6 compared to the CLP + saline group ($p = 0.001$). Furthermore, the levels of IL-10 were significantly increased in both brain and serum in the CLP + vit C group compared to the CLP + saline group ($p = 0.001$).

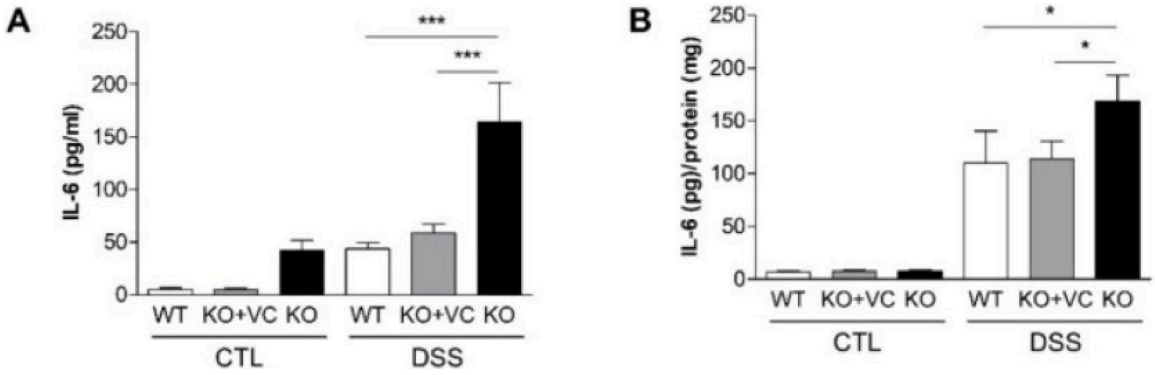

Fig. 8. The graph adapted from Hyejung et al. (2022) [71] illustrates the impact of vitamin C deficiency and dextran sulfate sodium (DSS) treatment on IL-6 levels. After 7 days of DSS treatment, IL-6 levels were measured in both plasma (A) ($n = 15–18$) and colon homogenates (B) ($n = 9–13$) using ELISA. The graph indicates a significant increase in IL-6 levels in both vitamin C deficiency and DSS treatment groups. Statistical significance is denoted by * for $p < 0.05$ and *** for $p < 0.001$.

Vitamin C and IL-6 in rats

Ningzhang et al. [70] utilized 61 septic rat models weighing 200–250 g and aged 6–8 weeks to investigate the impact of vitamin C on IL-6 levels. Using a cecal ligation puncture (CLP) septic model, rats were divided into three groups: saline + sham ($n = 11$), saline + CLP ($n = 25$), and CLP + high-dose vitamin C (200 mg/kg) ($n = 25$). After 7 days of sepsis, the survival rate was higher in the vitamin *C* + CLP group compared to the saline + CLP group (58.8 % vs 47.1 %). IL-6 levels were measured 24 hours post-surgery in both serum and brain, revealing higher levels in both saline + CLP and vitamin *C* + CLP groups compared to the Sham group ($p < 0.001$). However, significantly lower IL-6 levels were found in the vitamin *C* + CLP group compared to the saline + CLP group ($p = 0.001$). Additionally, TNF-alpha and anti-inflammatory cytokine IL-10 levels were measured in serum and brain 3 hours post-surgery, showing higher TNF-alpha and IL-6 levels in the saline +

CLP group, while IL-10 levels were significantly lower in the vitamin *C* + CLP group, as shown in Fig. 7.

In another study by Hyejung et al. (2022) [71], mouse models with acute colitis were used to explore the effect of vitamin C on inflammatory markers induced by dextran sulfate sodium (DSS) administration. The mice were categorized into wild-type (WT), vitamin C-deficient Gulo-/- mice (KO), and vitamin C-sufficient Gulo-/- mice (KO+VC). The KO mice exhibited the highest mortality rate (26 % for KO, 3 % for WT, and 6 % for KO+VC). IL-6 levels were notably elevated in KO mice after 7 days, with the highest production observed in the KO+DSS group compared to other groups. Vitamin C supplementation was found to reduce IL-6 production in mice with acute colitis compared to vitamin C-deficient mice suffering from the same condition, as shown in Fig. 6.

Discussion

Vitamin C and lipoprotein(a)

The animal studies conducted on the relationship between vitamin C and lipoprotein(a) (lp(a)) deposition in atherosclerosis have revealed compelling insights. In both guinea pigs and transgenic mice deficient in vitamin C, increased lp(a) infiltration into the vascular wall was observed, leading to atherosclerotic plaque development. Conversely, when guinea pigs were supplemented with adequate vitamin C, Atherosclerotic plaques, along with lp(a) deposition, were notably absent. This suggests a crucial role for vitamin C in maintaining endothelial matrix integrity and preventing atherosclerosis [68,69].

Interestingly, the animal models lacking the ability to synthesize vitamin C and produce human lp(a) further supported these findings. In hypoascorbemic conditions, increased lp(a) accumulation in the vascular wall was observed, while supplementation with high doses of vitamin C prevented lp(a) deposition. These results highlight the importance of sufficient ascorbate levels in inhibiting lp(a) infiltration and preserving vascular wall integrity [68].

However, human studies have not consistently demonstrated an inverse relationship between vitamin C supplementation and plasma lp(a) levels. Despite this, vitamin C supplementation has shown efficacy in reducing other lipids and triglycerides, indicating its potential cardiovascular benefits [72]. Conversely, niacin (Niacin) supplementation has been found to lower lp(a) levels significantly [73].

In summary, while animal studies underscore the importance of vitamin C in preventing lp(a) deposition and atherosclerosis, human studies present a more nuanced picture. Further research is needed to elucidate the mechanisms underlying the discrepancy between animal and human studies and to explore alternative therapeutic strategies for reducing lp(a) levels and mitigating cardiovascular risk.

Vitamin C and IL-6

In septic rats, vitamin C supplementation has been shown to reduce serum IL-6 levels, along with TNF-α, and increase anti-inflammatory cytokine IL-10 concentration. Vitamin C's modulation of the Nrf2 pathway is pivotal in maintaining cellular redox balance and attenuating atherosclerotic progression. By upregulating total and nuclear Nrf2 expression, as well as enhancing HO-1 protein expression, vitamin C exerts protective effects against plaque development [70]. Animal studies have consistently demonstrated improvements in inflammatory biomarkers with vitamin C supplementation, and similar results have been observed in human studies.

Human trials have reported significant reductions in hsCRP and IL-6 levels following vitamin C intervention [63,64]. Peluso et al. [74] found that vitamin C-rich fruit juice reduced postprandial stress in obese individuals by decreasing IL-6 and TNF-α levels. Mikirova et al. [75] demonstrated a reduction in hsCRP levels with vitamin C supplementation in individuals with low serum ascorbate. Intravenous ascorbate administration has also been linked to decreased plasma CRP levels and improved cancer outcomes. Gutirrez et al. [76], in 2013, experimented with DM patients and observed that 500–1000 mg/day of vitamin C supplementation for a short period has an inverse effect on atherosclerosis development in diabetes patients by affecting IL-6. Ferron-Elma et al. [77] also observed a significant reduction in IL-6 concentration in 2012 after a 450 mg/day intervention of vitamin C in patients who had sepsis and abdominal surgery.

Cross-sectional studies have revealed an inverse relationship between plasma ascorbate levels and inflammatory markers, with lower CRP and IL-6 levels associated with higher plasma ascorbate concentrations [78]. This inverse association extends to the risk of heart failure, where higher vitamin C levels correlate with reduced risk, potentially mediated by decreased CRP and IL-6 levels [79].

Effect of vitamin C on fibrinolysis

The findings from this review strongly support the potential therapeutic role of vitamin C in improving fibrinolytic activities. Studies have consistently demonstrated that even a single dose of vitamin C can significantly enhance fibrinolysis, with long-term supplementation maintaining fibrinolytic activity levels at about 50 % above control levels in patients with coronary events [65–67].

Research by Woodhouse et al. [80] revealed an inverse relationship between low serum ascorbate levels and increased PAI-1 activity, a critical indicator of future cardiac events. Further studies confirmed that vitamin C intake significantly reduces PAI-1 levels in coronary and diabetic patients [65,66]. Combinations of vitamin C and E have also been effective in reducing PAI-1 levels, as demonstrated in patients with conditions like pre-eclampsia [81] and in animal models fed a high-cholesterol diet [82,87].

While high tPA levels are associated with atherosclerosis, vitamin C administration has shown an inverse relation with tPA levels in some studies [83]. In-vitro studies have demonstrated that vitamin C can increase tPA secretion, although conflicting results exist regarding its impact on tPA levels in vivo [88]. Other fibrinolysis factors such as fV, fVII, ATIII, and uPA were not significantly affected by vitamin C supplementation in the reviewed studies [63].

In addition to enhancing fibrinolytic activities, vitamin C also inhibits platelet adhesion to lesion sites and prevents monocyte adhesion to the endothelium by 27 % in coronary artery patients [65]. Animal models have shown that vitamin C can reduce leukocyte adhesion to the endothelium induced by cigarette smoke, further underscoring its potential protective role [84]. Moreover, vitamin C supplementation may prevent vascular smooth muscle cell apoptosis, providing additional stability to plaques [85].

While the recommended daily dosage of vitamin C is typically 40 mg, doses ranging from 500 mg to 2000 mg/day have shown significant benefits in the reviewed studies, with higher doses not necessarily associated with additional benefits [63–67]. Matthias Rath and Linus Pauling suggested higher dosages, but the efficacy of such high doses remains uncertain. The evidence presented in this review supports the potential therapeutic role of vitamin C in improving fibrinolytic

activities and mitigating cardiovascular risk factors.

Limitations: While our review provides valuable insights into the relationship between vitamin C supplementation and lp(a) levels, it is important to acknowledge its limitations. One notable limitation is the relatively small sample size in human trials, which may affect the generalizability of our findings. Additionally, the focus of animal studies on lp(a) accumulation in hypoascorbemic conditions contrasts with the emphasis on serum lp(a) levels in human studies included in our review. This disparity highlights the need for further research to elucidate the specific effects of vitamin C supplementation on lp(a) deposition on the endothelial wall in humans.

Furthermore, the articles included in our review lack exploration of genetic influences on lp(a) levels and interleukin-6 (IL-6) production, which could potentially confound the observed associations. Moreover, important confounders such as dietary factors, liver health, and daily fat intake were not consistently accounted for in the studies reviewed, which may limit the interpretation of our findings. Additionally, the absence of animal studies investigating the relationship between fibrinolysis and vitamin C further underscores the need for comprehensive research in this area.

Despite these limitations, our review contributes valuable insights into the potential impact of vitamin C supplementation on lp(a) levels and cardiovascular health. Future studies addressing these limitations and incorporating a broader range of factors will be essential for advancing our understanding of the complex interplay between vitamin C, lp(a), and cardiovascular risk.

Conclusion

The study provides a significant contribution to the understanding of vitamin C's role in combating atherosclerosis, underscoring its potential as a therapeutic agent in cardiovascular disease management. Through a comprehensive review of both animal and human studies, the research elucidates how vitamin C supplementation can positively affect key factors involved in atherosclerotic progression, notably by reducing lipoprotein(a) levels, decreasing interleukin-6 concentrations, and enhancing fibrinolytic activity. These findings highlight the antioxidant and anti-inflammatory properties of vitamin C, offering insights into its mechanism of action in cardiovascular protection.

This study not only reinforces the importance of vitamin C in cardiovascular health but also opens avenues for future research into its potential benefits across a broader spectrum of inflammatory and oxidative stress-related conditions. The integration of vitamin C into preventive and therapeutic strategies for atherosclerosis could significantly impact public health, emphasizing the need for a holistic approach to cardiovascular disease management that includes dietary and lifestyle modifications alongside conventional medical treatments.

Ethical consideration

No ethics approval was required.

Registration and protocol

This review is not registered.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author used a free version of chat GPT 3.5 in order to paraphrase and improve the vocabulary and readability of the manuscript. After using the chat GPT, the author reviewed and edited the content as needed and took full responsibility for the content of the publication.

CRediT authorship contribution statement

Chetan Sharma: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing – original draft, Visualization. **Dr. Claire Williams:** Supervision, Writing – review & editing, Methodology, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Claire Williams reports article publishing charges will be provided by the University of Sheffield institutional open access funds. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No new data were generated or analyzed during this study. All data included in this systematic review are derived from published literature available through databases such as PubMed, Cochrane Library, and Google Scholar, and are cited appropriately within the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hsr.2025.100230.

Appendices

Appendix A.

Type of bias	Domain	Description of domain	Review authors judgment
Selection bias	Sequence generation	Describe the methods used, if any, to generate the allocation sequence in sufficient detail to allow an assessment whether it should produce comparable groups.	Was the allocation sequence adequately generated and applied? (*)
Selection bias	Baseline characteristics	Describe all the possible prognostic factors or animal characteristics, if any, that are compared in order to judge whether or not intervention and control groups were similar at the start of the experiment.	Were the groups similar at baseline or were they adjusted for confounders in the analysis?
Selection bias	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment.	Was the allocation adequately concealed? (*)
Performance bias	Random housing	Describe all measures used, if any, to house the animals randomly within the animal room.	Were the animals randomly housed during the experiment?
Performance bias	Blinding	Describe all measures used, if any, to blind trial caregivers and researchers from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?
Detection bias	Random outcome assessment	Describe whether or not animals were selected at random for outcome assessment, and which methods to select the animals, if any, were used.	Were animals selected at random for outcome assessment?
Detection bias	Blinding	Describe all measures used, if any, to blind outcome assessors from knowing which intervention each animal received. Provide any information relating to whether the intended blinding was effective.	Was the outcome assessor blinded?
Attrition bias	Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized animals), reasons for attrition or exclusions, and any re-inclusions in analyses for the review.	Were incomplete outcome data adequately addressed? (*)
Reporting bias	Selective outcome reporting	State how selective outcome reporting was examined and what was found.	Are reports of the study free of selective outcome reporting? (*)
Other	Other sources of bias	State any important concerns about bias not covered by other domains in the tool.	Was the study apparently free of other problems that could result in high risk of bias? (*).

Section and Topic	Item #	Checklist item	reported on page:
TITLE			
Title	1	Identify the report as a systematic review.	1

(continued on next page)

(*continued*)

Section and Topic	Item #	Checklist item	reported on page:
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3–10
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	10–11
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	11–12
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	11–12
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	13
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	14
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	13–14
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	14
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	15
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	13–14
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	14
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	16
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	13
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	13–14
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	16
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	16–23
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	16–23
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	16–23
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	17–23
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	16–23
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23–26
	23b	Discuss any limitations of the evidence included in the review.	26
	23c	Discuss any limitations of the review processes used.	26
	23d	Discuss implications of the results for practice, policy, and future research.	26–27
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	27
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	27
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	27
Competing interests	26	Declare any competing interests of review authors.	NA
Availability of data, code a*nd other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	29–36

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. 10.1136/bmj.n71.

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